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Article

Toward the Total Synthesis of Alpkinidine: Synthesis of Haloquinone CE Ring System Synthons and Attempted Nucleophilic Bisannulation

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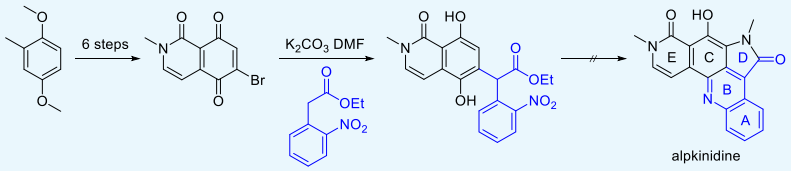

ABSTRACT: Model chemistry involving the bisannulation of 2,3-dichloro-1,4-naphthoquinone with the ester enolate derived from ethyl *o*-nitrophenylacetic acid, which rapid assembled the ABCD ring system of a pentacyclic pyrroloacridine, has been applied to the attempted synthesis of the marine natural product alpkinidine. The reaction of ethyl *o*-nitrophenylacetic acid with 6,7-dichloro-2-methylisoquinoline-1,5,8(2*H*)-trione, required to extend the model strategy to alpkinidine, was unfruitful, giving only complex mixtures. Efforts to direct the regiochemistry of the key Michael substitution step using 6-bromo-2-methylisoquinoline-1,5,8(2*H*)-trione afforded an adduct sharing the complete carbon skeleton of alpkinidine, but this could not be elaborated to the natural product.

INTRODUCTION

The natural product alpkinidine (**1**) (Figure 1), which was isolated from the Indonesian marine sponge *Xestospongia carbonaria* in 2002,[1] is the only D-ring-oxygenated member of a small class of alkaloids possessing a rare pyrroloacridine core. The other congeners, plakinidines A−E (**2**−**6**), were also obtained from Indo-Pacific sponges[2−4] and ascidians,[5,6] although their biosynthetic origin is likely microbial.[5]

Alpkinidine was shown to be selectively toxic to solid tumor-derived cell lines over normal cells,[1] and the plakinidines are cytotoxic to a variety of cancer cell lines.[4] Plakinidines A and B also have anthelmintic activity.[2] However, assessment of the biological activity of the pyrroloacridines is limited, presumably due to material scarcity. In contrast, the related pyridoacridines have been widely studied. Nearly all are cytotoxic as a result of their interactions with DNA,[7] and a range of other biological activities have been described, including antibiotic,[8] antifungal,[9] antiviral,[10] antiparasitic,[11] insecticidal,[12] and antitumor.[13] Neoamphimedine (**7**) (Figure 1), which is a cometabolite of alpkinidine in *X. carbonaria*,[1] is of particular relevance due to its structural similarity to alpkinidine and its promising biological activity. An inhibitor of DNA topoisomerase IIα, neoamphimedine (**7**), is cytotoxic to yeast and a wide variety of mammalian cell lines.[1,14−16] In one study, it was equipotent with the clinical chemotherapeutic etoposide at inhibiting the growth of xenograft tumors in mice,[16] making it a lead compound for cancer chemotherapy.

The potential for useful biological activity and the unique structures of pyrroloacridine natural products have attracted the interest of several synthetic chemists. In 2004, Kitahara et al.[17] reported the synthesis of a hybrid pyrroloacridine **9** possessing the D ring of alpkinidine and the E ring of plakinidine C, but lacking the C7 substituent present in the natural products, in nine steps from **8** (Scheme 1). Beginning with *o*-aminoacetophenone (**10**), Fukuyama and co-workers detailed a 20-step synthesis of a similar hybrid, **11**, which is nitrogenated at C7 but has an incompletely elaborated E ring.[18] Tokuyama et al. have also tackled the plakinidine core, achieving the synthesis of a partially reduced ABCD ring system **13** in 10 steps from precursor **12**.[19]

We previously reported the concise synthesis of the model compound **21**, containing the ABCD ring system of alpkinidine, from 2,3-dichloronaphthoquinone (**14**) (Scheme 2).[20] Conjugate substitution with the carbanions derived from ethyl *o*-nitrophenylacetate (**15**) or protected oxindole **16** gave intermediates **17** and **18**, respectively. A cascade reaction involving conjugate substitution of methylamine, then

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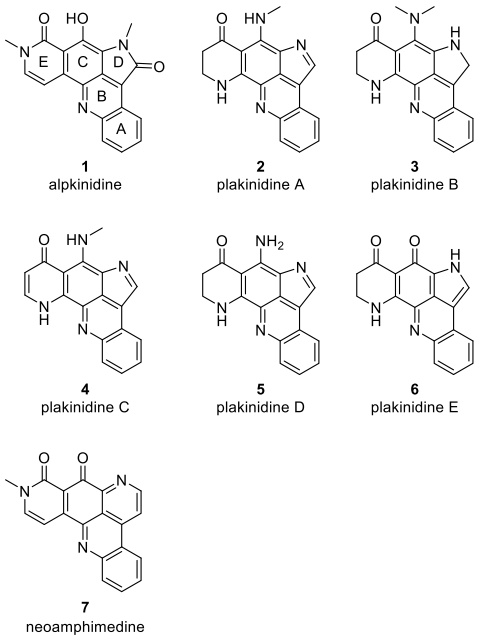
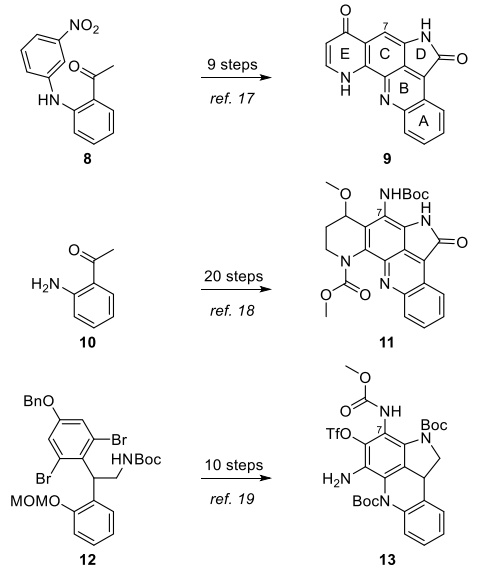


Figure 1. Structures of alpkinidine and related marine alkaloids.

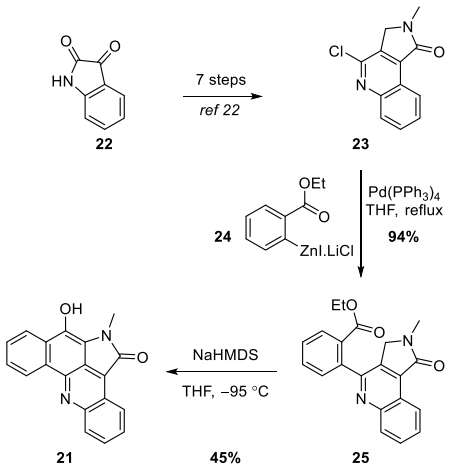
Scheme 1. Previous Syntheses of Pyrroloacridines Related to Alpkinidine and the Plakinidines



intramolecular acyl transfer, provided lactams **19** and **20**, which upon unmasking of the anilino group, cyclodehydrated to give **21**.

Tilve and co-workers subsequently developed a synthesis of **21** (Scheme 3).[21] The quinolyl chloride **23**, prepared from

Scheme 3. Tilve and Co-Workers' Synthesis of 21[21]



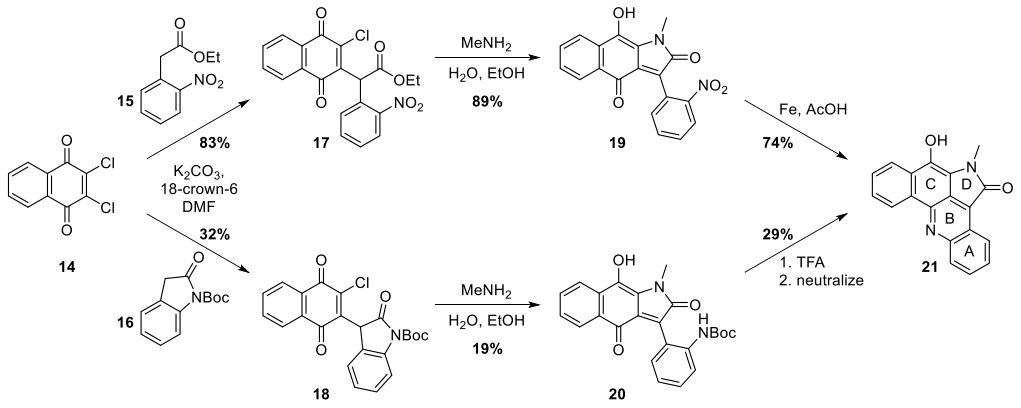
isatin (**22**) in seven steps,[22] underwent a high-yielding Negishi coupling with arylzinc **24** to give biaryl **25**. Dieckmann-like condensation then provided the target pentacycle **21**.

Herein, we provide a full account of our efforts to develop and apply the model chemistry depicted in Scheme 2 to the synthesis of alpkinidine.

RESULTS AND DISCUSSION

Model Chemistry. Our initial objective for this project was to efficiently access the ABCD ring system of alpkinidine. We established that this was possible through the chemistry depicted in Scheme 4.[20] Conjugate substitution of 2,3-dichloronaphthoquinone (**14**) with the carbanion derived from nitrile **26**, followed by treatment of the resultant adduct **27** with methylamine, afforded aminopyrrole **28**. Reductive cyclization followed by aerial oxidation provided pentacycle **29**, with the same ABCD ring scaffold as alpkinidine. However, attempts to oxodeaminate **29** to give the required pyrrolone D ring were unsuccessful. Hence, subsequent

Scheme 2. Construction of the ABCD Ring System of Alpkinidine[20]



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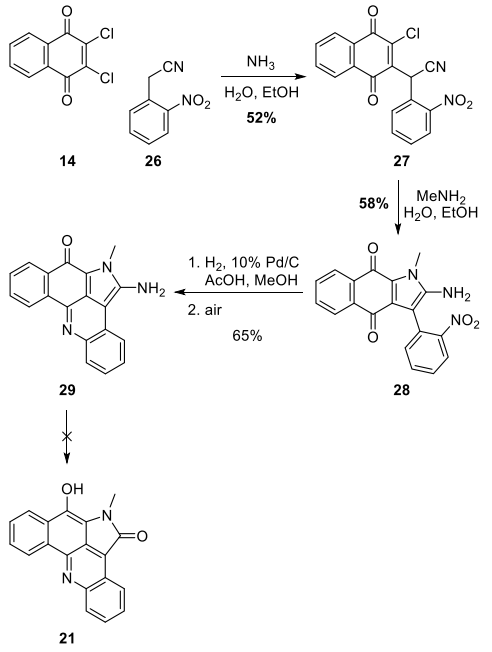
Scheme 4. First Route to the ABCD Ring System of Alpkinidine[20]



efforts focussed on nucleophiles that would more directly provide the D ring carbonyl group.

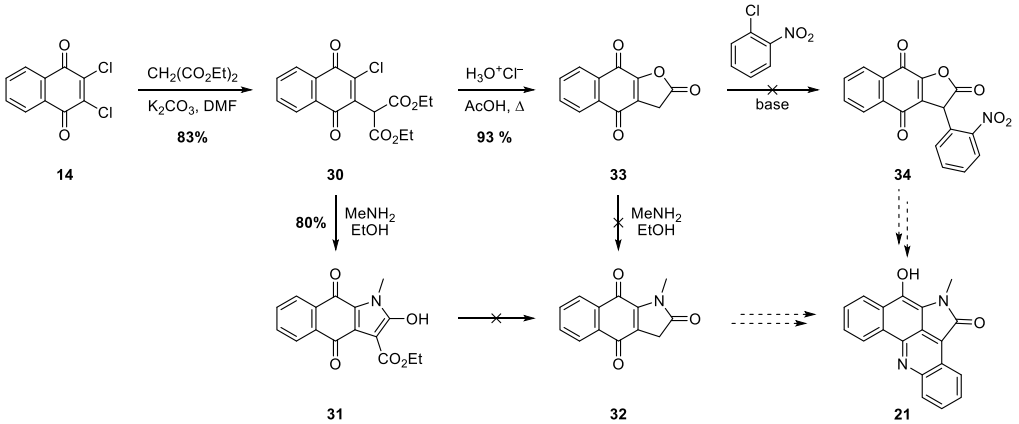
The reaction of **14** with diethyl malonate/sodium ethoxide was previously reported to give Michael substitution product **30** in only 27% yield.[23] However, with a milder base in an aprotic solvent, the efficiency of this reaction was improved considerably (Scheme 5). Two lines of investigation were explored for the elaboration of adduct **30**. First, substitution/lactamization with methylamine to give hydroxypyrrole **31** proceeded smoothly, as expected based on similar precedents.[24,25] However, failure to effectively decarboxylate **31** to give **32** under a variety of conditions thwarted efforts to advance this intermediate. In contrast, acid-catalyzed decarboxylation/cyclization of **30** provided lactone **33** in good yield, but subsequent treatment with methylamine failed to give pyrrolone **32**. Nucleophilic aromatic substitution of *o*-chloronitrobenzene with the carbanion derived from lactone **33** was also investigated but gave a complex mixture of products under a variety of conditions.

Attention then turned to the reaction of **14** with enolate nucleophiles already incorporating the A ring of alpkinidine. As mentioned in the Introduction section, this line of investigation was fruitful, providing two rapid approaches to the model compound **21** (Scheme 2). The reaction of intermediate **17** with other primary amines was also briefly investigated, providing the *N*-2-hydroxyethyl **35** and *N*-benzyl **36** analogues (Scheme 6). In the former case, the crude yield was good, but major losses during purification led to low recovery. An X-ray crystal structure of **35** was obtained (Scheme 6), revealing that the C2−O and C9−O bonds are of similar length and intermediate between standard phenolic C−OH and carbonyl bond lengths, as one might expect for the highly conjugated system. The position of the phenolic hydrogen was not placed, so tautomeric structure **35a** cannot be ruled out, and ergo, **36a** may also be a better representation than **36**. The *N*-benzylpyrrolone **36** underwent reductive cyclization as expected to provide pentacycle **37**. Like the *N*-methyl analogue **21**,[20] **37** was unstable in dimethyl sulfoxide (DMSO)/air but was able to be fully characterized before substantial decomposition occurred.

Toward Alpkinidine. Application of the methodology described above to the synthesis of alpkinidine required dichloroisoquinolinetrione **38** (Scheme 7). The reduced symmetry of **38**, compared to that of 1,2-dichloronaphthoquinone (**14**), necessitated a regioselective Michael substitution reaction with the enolate derived from **15**, that is, to provide **39** preferentially. Simple resonance arguments suggest that C7 is likely the more electrophilic of the two chlorinated quinonoid carbons. Nevertheless, taking advantage of the chelating *peri*-dicarbonyl moiety with Lewis acid activation, it might be possible to reverse any such inherent bias. Should **39** be procured, it was anticipated that elaboration to alpkinidine (**1**) via **40** would proceed smoothly, based on the model chemistry.

The synthesis of dichloroquinone **38** began with the commercial benzoic acid **41** (Scheme 8), which may also be conveniently prepared from the cheaper 2,5-dimethoxybenzaldehyde.[26] Conversion to the acid chloride was followed by coupling with secondary amine **42**, prepared in excellent yield by treatment of bromoacetal with excess methylamine. The resulting tertiary amide **43** underwent clean Pomeranz−Fritsch-like cyclization/aromatization[27] to provide isoquinolone **44**. Attempted oxidative demethylation of **44** with ceric ammonium nitrate (CAN) gave an intractable mixture of

Scheme 5. Preliminary Efforts to Generate the D Ring of Alpkinidine



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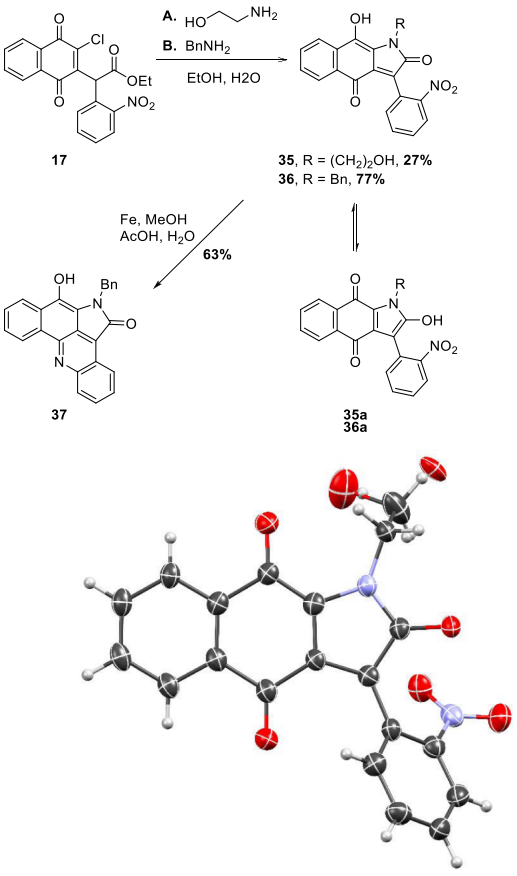
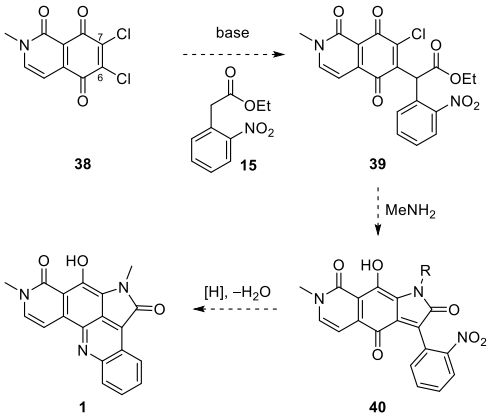
Scheme 6. Elaboration of 17 with Different Amines, Including a Representation of the X-Ray Crystal Structure of 35/35a[a]



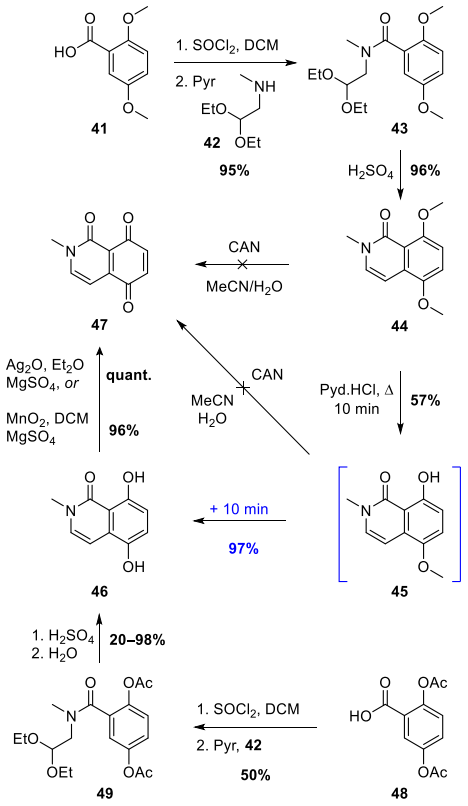
[a]The position of the phenolic proton in **35/35a** could not be defined. The molecule is disordered about the ethanolamine portion, with two distinct alcohol environments being calculated for both with an associated molecule of MeOH (omitted for clarity). Displacement envelopes are at 50% probability amplitude, with hydrogen atoms assigned arbitrary radii.

Scheme 7. Key Precursor 38 and Proposed Route to Alpkinidine



products; hence, stepwise demethylation then oxidation was pursued. A short treatment with molten pyridinium chloride[28,29] (to avoid N-demethylation) provided monomethyl ether **45** in moderate yield, but again, CAN-mediated oxidative demethylation of this phenol was unsuccessful.

Scheme 8. Synthesis of Quinone 47



Fortunately, a slightly longer Prey demethylation allowed very efficient conversion to hydroquinone **46**, and quantitative oxidation to quinone **47** was achieved with silver(I) oxide.[30,31] Subsequently, MnO_2[32] was found to be nearly as effective for this oxidation.

In an effort to circumvent the demethylation step, 2,5-diacetoxybenzoic acid (**48**)[33] was amidated to give **49**, which cyclized in concentrated sulfuric acid and deacetylated during aqueous work-up, providing hydroquinone **46**. On one occasion, this cyclization gave a near quantitative yield of **46**. However, on repetition, much lower yields were obtained, perhaps due to variability in the water content of the sulfuric acid.

With **47** in hand, attention turned to the regioselective dichlorination of the quinone moiety. Shi et al.[34] converted quinone **50** to dichloride **51** using thionyl chloride/pyridine (Scheme 9). Under similar conditions, **47** gave mainly chlorohydroquinone **52a**, with a trace of the regioisomer **52b**. The formation of the hydroquinone likely reflects the greater reduction potential of the electron-deficient quinone **47** (and its monochlorinated derivatives), relative to **50/51**. The identity of the reductant is unclear, but may be sulfur monoxide, a byproduct of the chlorination reaction.[34] The mixture of hydroquinones **52a/b** was oxidized, and X-ray crystallography revealed a 94:6 cocrystal of quinones **53a/b**, respectively (Scheme 9).

Quinone **47** reacted with sulfuryl chloride/triethylamine[35] to give the desired dichloride **38**, albeit in very poor yield, accompanied by trichloride **54** and an intractable mixture of other products (Scheme 10). Nevertheless, this provided enough material to test the key Michael substitution reaction. Alas, the reaction of **38** with the carbanion derived from ethyl *o*-nitrophenylacetate (**15**) gave none of the expected adduct

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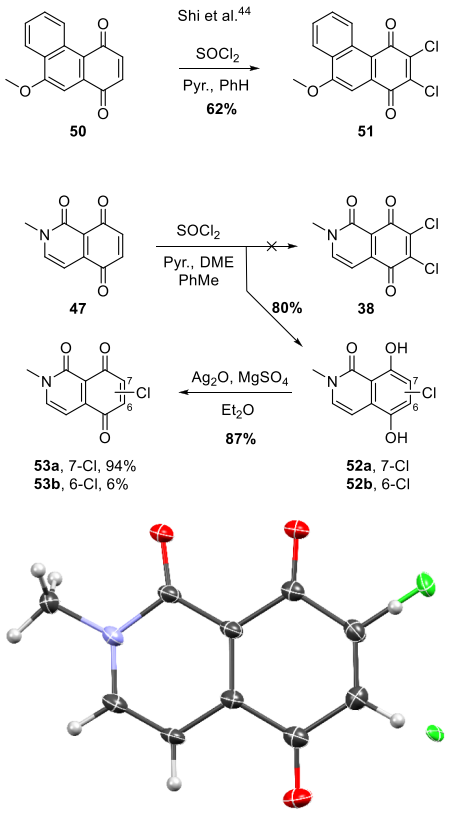
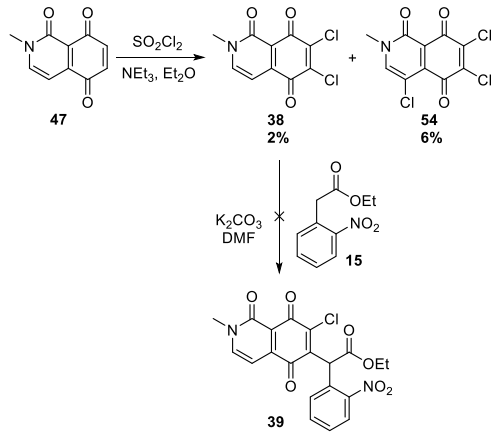
Scheme 9. Attempted Synthesis of 38, Including a Representation of the X-ray Crystal Structure of 53a/b (a 94:6 Cocrystal Structure)[a]



[a]Displacement envelopes are at 50% probability amplitude with hydrogen atoms assigned arbitrary radii.

Scheme 10. Low Yielding Chlorination and Failed Michael Substitution



39. No other identifiable products were observed, providing little information as to why this reaction failed when the model chemistry (Scheme 2) worked so well.

In an attempt to salvage this route and address the regiochemical challenge in linking the CE and ABD ring systems of alpkinidine, monohalogenated quinones, in which the halogen could direct Michael substitution to the 6-position, were targeted. Both bromide **67** and iodide **68** were prepared to test this hypothesis, as outlined in Scheme 11. Bromination or iodination[36] of commercial 2,5-dimethoxytoluene (**55**) gave **56**[37] and **57**, respectively. Permanganate oxidation to benzoic acids **58**[38]/**59** was followed by amidation of the derived acid chlorides with methylaminoacetal **42**, providing **60**/**61**, respectively. Cyclization with sulfuric acid to give isoquinolones **62**/**63** was complicated by partial, regioselective demethylation, also affording **64**/**65**, respectively. The structure of bromide **64** was confirmed by X-ray crystallography. The halogens clearly play a role here as no such demethylation was observed in reaction of the nonhalogenated analogue (**43** → **44**, Scheme 8). Precedents for similar demethylations of *ortho*-bromoanisoles by sulfuric acid exist.[39−41] While initially annoying, this side reaction turned out to be fortuitous as attempts to oxidatively demethylate **62**/**63** gave complex mixtures of indiscernible products and efforts to fully demethylate iodide **63** under more standard conditions were similarly unsuccessful. In contrast, oxidative demethylation of monomethyl ethers **64**/**65** gave acceptable yields of the target quinones **67**/**68**, respectively. Interestingly, iodide **68** crystallized from DMSO-d_6 solution (NMR sample) as a monosolvate exhibiting halogen bonding (Scheme 11).

Unfortunately, the reaction of iodide **68** with ethyl *o*-nitrophenyl acetate (**15**) under basic conditions furnished neither the expected Michael substitution product **69** (Scheme 12) nor any other identifiable compounds. In contrast, the corresponding reaction of bromide **67** gave a discrete new spot by TLC. However, upon isolation, this product was identified as hydroquinone **70**, which presumably arises by reduction of the expected Michael substitution product **69**. The nature of the reductant can only be speculated upon, as no other products could be isolated or identified among the complex mixture. Reactions of bromoquinones with C-nucleophiles are known to be complicated by *cine* addition competing with *ipso*-substitution.[42−47] Thus, *cine* addition of the carbanion derived from **15** to **67** would give rise to hydroquinone **71**, which could reduce the *ipso* substitution product **69** to **70**. The byproduct, quinone **72**, might then take part in subsequent reactions, giving rise to the complex mixture of products observed.

Despite the low yield, the production of **70** was a promising advance in developing a synthesis of alpkinidine using our bisannulation strategy. Hence, **70** was oxidized with silver(I) oxide with the expectation that quinone **73** might be elaborated to alpkinidine (**1**) (Scheme 13). However, **73** was not detected in the crude product of this reaction, as evidenced by the lack of a quinonoid methine resonance in the ^{1}H NMR spectrum. The appearance of a downfield signal, consistent with a hydrogen-bonded phenolic hydroxyl, suggests that quinone **73** might have tautomerized to *o*-quinonemethide **74** (and or its *Z* isomer), but scarcity of material prevented conclusive identification of this product. Indeed, this complication, along with the disappointing yield of the previous step, and the perceived difficulty in carrying **74** forward to alpkinidine, made this route unappealing, and hence, it was abandoned.

CONCLUSIONS

Two approaches to connect the CE ring system and A ring of the pentacyclic pyrroloacridine natural product alpkinidine (**1**), through construction of the BD rings using Michael substitution of haloquinonoid isoquinolinetriones, have been explored (Scheme 14). Chemistry that efficiently afforded the

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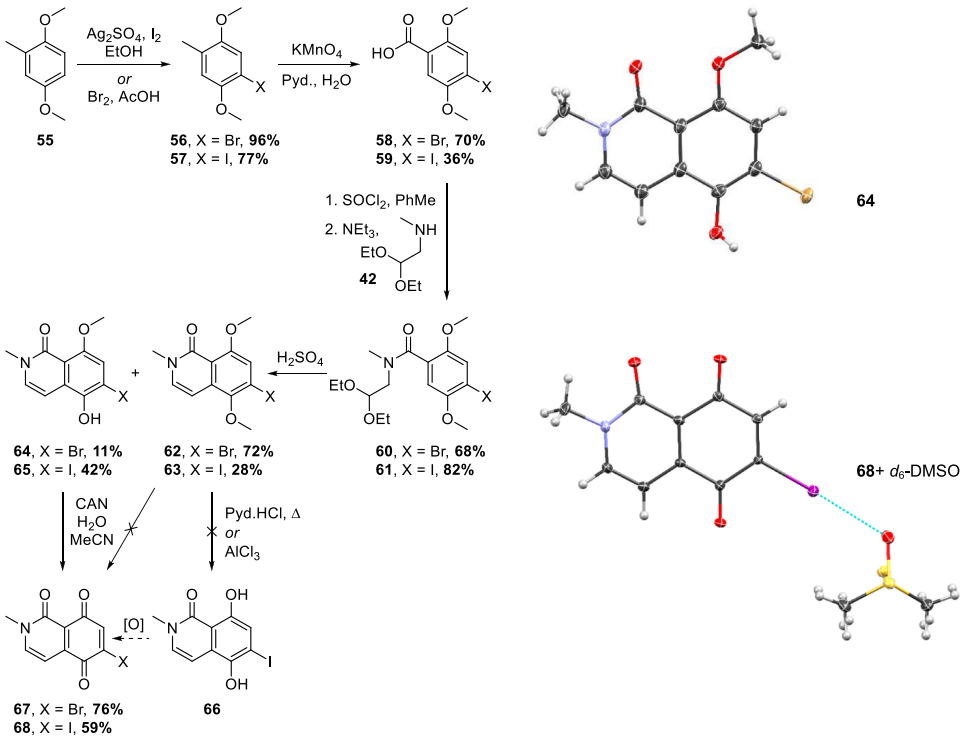
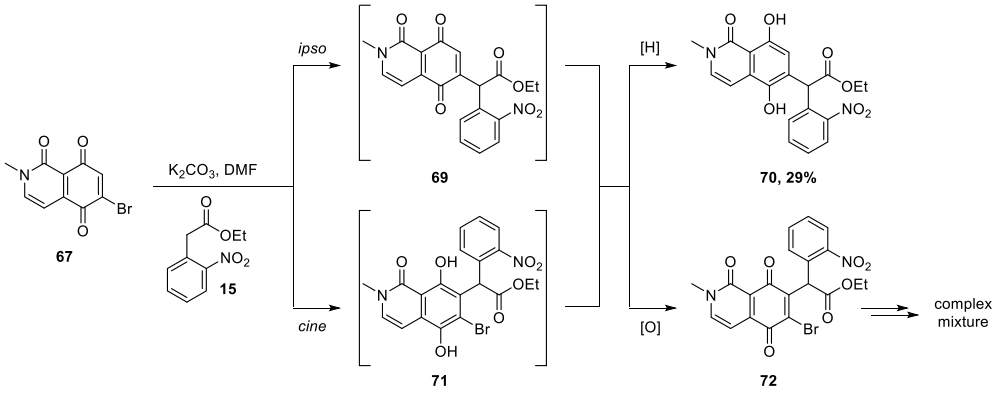
Scheme 11. Synthesis of 6-Haloisoquinolinetriones, including Representations of the X-Ray Crystal Structures of 64 and 68[a]



[a]Displacement envelopes are at 50% probability amplitude with hydrogen/deuterium atoms assigned arbitrary radii. The I···O halogen bond between **68** and DMSO-d_6 is indicated in light blue.

Scheme 12. Unexpected Reductive Substitution of and Hypothetical Competing *Cine* Addition to 67



model pentacyclic pyrroloacridine **21**, lacking only the E ring of alpkinidine, failed to translate to the "real system". The novel isoquinolinetrione **47**, which may also prove useful for the synthesis of neoamphimedine and analogues, was prepared efficiently. This intermediate could be chlorinated, albeit in very low yield, but reactions of dichloroquinone **38** with **15** under basic conditions gave only complex mixtures.

Attempts to direct the regiochemistry of Michael substitution reactions using 6-haloisoquinolinetriones (e.g., **67**) were also explored. This strategy afforded adduct **70**, comprising the complete carbon-connectivity of alpkinidine (**1**). However, attempts to elaborate this scaffold to the required heterocyclic ring system failed.

Given these setbacks, our attention turned to Michael additions (as opposed to substitutions) to construct the key carbon−carbon bond that is ultimately shared by the BD rings in alpkinidine (**1**). These endeavors are reported in the following paper.

EXPERIMENTAL SECTION

General. General experimental details are as reported previously.[20,48]

Synthesis. *Diethyl 2-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)malonate (**30**).*[23] 2,3-Dichloro-1,4-naphthoquinone (**14**) (1.14 g, 5.03 mmol) was added to a stirred suspension of diethylmalonate (1.6 mL, 10 mmol) and K_2CO_3 (1.4 g, 10 mmol) in dimethylformamide (DMF) (80 mL) and heated to 45 °C. After 1.5 h, the reaction mixture was cooled, acidified with 1 M HCl (20 mL), extracted with EtOAc (3 × 20 mL), dried and evaporated, and the crude residue was subjected to chromatography. Elution with 1:9 EtOAc/hexanes gave **30** (1.46 g, 83%) as a pale green solid, mp 102−104 °C [lit.[23] 102 °C]. ^{1}H NMR (400 MHz,

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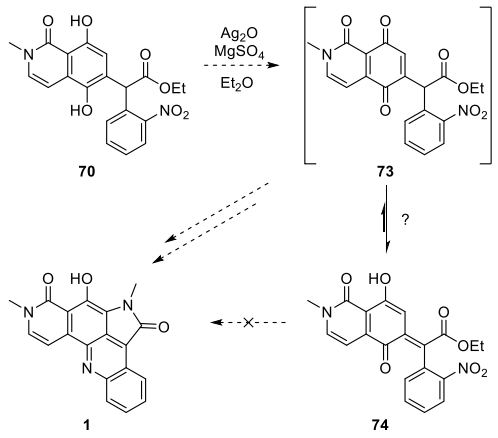
Scheme 13. Oxidation of Hydroquinone 70 and Putative Tautomerization Preventing the Formation of the Alpkinidine D Ring



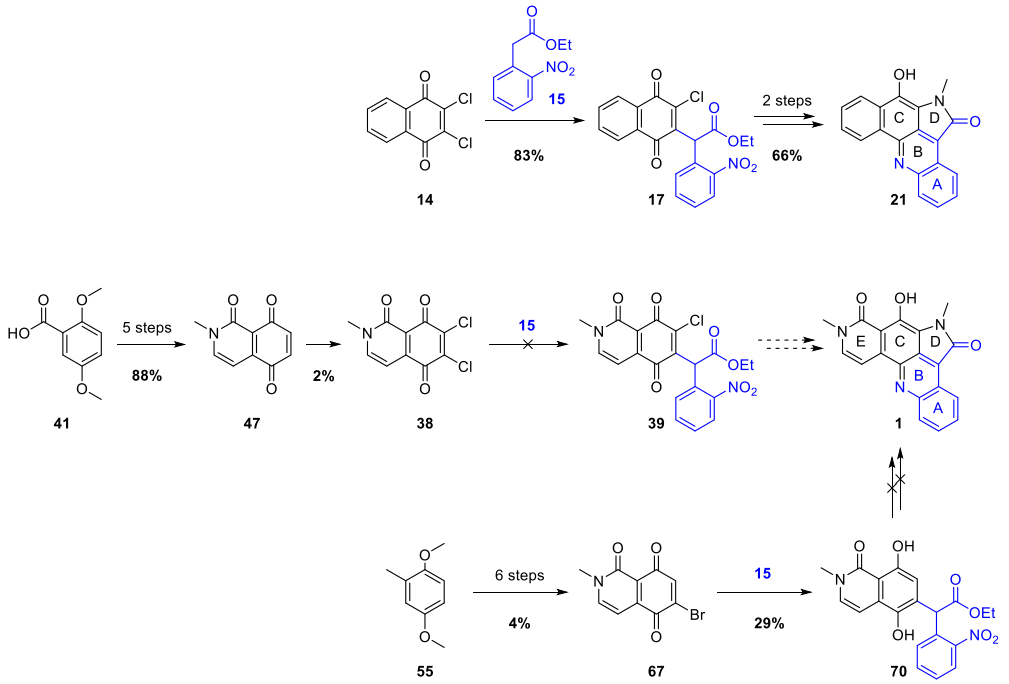
$CDCl_3$): δ 8.21−8.12 (m, 2H, 2× ArH), 7.82−7.76 (m, 2H, 2× ArH), 5.12 (s, 1H, H2), 4.32−4.23 (m [app dq], 4H, 2× CH_2), 1.28 (t, J = 7.1 Hz, 6H, 2× CH_3). The ^{1}H NMR data were consistent with the literature.[23]

*Ethyl 2-Hydroxy-1-methyl-4,9-dioxo-4,9-dihydro-1H-benzo[f]indole-3-carboxylate (**31**).* Ethanolic $MeNH_2$ (0.13 mL, 1.04 mmol) was added to a solution of **30** (0.17 g, 0.50 mmol) in EtOH (5 mL) at 0 °C. After 1.5 h, the solution was poured into 1 M HCl (10 mL), extracted with EtOAc (3 × 10 mL), dried, and evaporated. The crude solid was precipitated from dichloromethane (DCM)/hexanes to give **31** (0.12 g, 83%) as a pale-yellow/orange solid. ^{1}H NMR (600 MHz): δ 11.4 (s, 1H, OH), 8.13 (m, 1H, H5 or H8), 8.07 (m, 1H, H5 or H8), 7.65 (m, 2H, H6 & H7), 4.70 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 3.93 (s, 3H, NMe), 1.50 (t, J = 7.2 Hz, 3H, OCH_2CH_3). ^{13}C NMR (150 MHz): δ 179.1 (C4 or C9), 176.2 (C4 or C9), 168.6 (CO_2), 159.3 (C2), 133.4 (C4a or C8a), 133.1 (C6 or C7), 132.9 (C6 or C7), 132.5 (C4a or C8a), 126.7 (C5 or C8), 125.5 (C5 or C8), 125.6 (C9a), 123.5 (C3a), 91.2 (C3), 61.7 (OCH_2CH_3), 30.8 (NMe), 14.3 (OCH_2CH_3). This compound was synthesized in 1930 from the bromide analogue of **30** and described as yellow needles.[49]

*Naphtho[2,3-b]furan-2,4,9(3H)-trione (**33**).* A suspension of **30** (0.44 g, 1.25 mmol) in AcOH (30 mL) and 6 M HCl (30 mL) was heated under reflux. After 24 h, the reaction mixture was cooled, neutralized with sat. aq $NaHCO_3$ (100 mL), extracted with EtOAc (5 × 20 mL), dried, and evaporated. The crude solid was then washed with DCM/hexanes to give **33** (0.25 g, 93%) as a brown solid, mp 240−245 °C. R_f (1:9 MeOH/DCM) 0.2. IR (ATR) ν_{max} cm^{-1}: 1704 (C═O), 1668 (C═O). ^{1}H NMR (600 MHz): δ 8.18 (m, 1H, ArH), 8.14 (m, 1H, ArH), 7.78 (m, 2H, ArH), 3.94 (s, 3H, H3). ^{13}C NMR (150 MHz): δ 181.7 (C4 or C9), 177.4 (C4 or C9), 172.9 (C2), 145.6 (C9a), 140.4 (C3a or C4a or C8a), 134.6 (ArH), 134.4 (ArH), 131.4 (C3a or C4a or C8a), 131.4 (C3a or C4a or C8a), 127.5 (ArH), 127.3 (ArH), 33.5 (C3). HRMS (APCI): calcd for $C_{12}H_7O_4^+$ [M + H]$^+$, 215.0348; found, 215.0339.

*9-Hydroxy-1-(2-hydroxyethyl)-3-(2-nitrophenyl)-1H,2H,4H-benzo[f]indole-2,4-dione (**35/35a**).* A solution of ethanolamine (0.15 mL, 2.48 mmol) in H_2O (1 mL) was added to a stirred solution of **17**[20] (0.11 g, 0.27 mmol) in EtOH (5 mL). After 30 min, the reaction mixture was diluted with aqueous 10% citric acid (20 mL) and extracted with EtOAc (3 × 10 mL). The organic phase was extracted with sat. aq $NaHCO_3$ (3 × 10 mL). The aqueous phase was acidified with 1 M HCl (50 mL), extracted with EtOAc (3 × 30 mL), dried, and evaporated to give **35**/**35a** (27 mg, 27%) as a purple solid, mp 122−125 °C. R_f (1:20:80 AcOH/MeOH/DCM) 0.3. IR (ATR) ν_{max} cm^{-1}: 3500−2500 (OH), 1712 (C═O), 1658 (C═O), 1630 (C═O). ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.09 (d, J = 8.4 Hz, 1H, ArH), 7.97 (d, J

Scheme 14. Summary of Key Approaches Investigated



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= 7.8 Hz, 1H, ArH), 7.79 (d, J = 7.2 Hz, 1H, ArH), 7.72 (m, 2H, ArH), 7.65 (dd [app. t], $J_1 = J_2$ = 7.2 Hz, 1H, ArH), 7.59 (dd [app. t], $J_1 = J_2$ = 7.2 Hz, 1H, ArH), 7.55 (d, J = 7.2 Hz, 1H, ArH), 4.46 (s, 1H, NCH_2), 4.40 (s, 1H, NCH_2), 3.72 (t, J = 6.6 Hz, 2H, CH_2O). ^{13}C NMR (150 MHz, DMSO-d_6): δ 180.4 (C4), 171.3 (C9), 151.1 (C2), 149.1 (C2′), 133.8 (CH), 133.7, 133.5 (CH), 132.9 (CH), 132.5, 128.5 (CH), 127.2, 125.5 (CH), 124.3 (CH), 123.7, 122.5, 101.6 (C3), 59.7 (CH_2), 45.4 (CH_2). HRMS (APCI): calcd for $C_{20}H_{15}N_2O_6^+$ $[M + H]^+$, 379.0939; found, 379.0925.

*1-Benzyl-9-hydroxy-3-(2-nitrophenyl)-1H,2H,4H-benzo[f]-indole-2,4-dione (**36/36a**).* A solution of benzylamine (0.30 mL, 2.7 mmol) in H_2O (1 mL) was added to a stirred solution of **17**[20] (0.11 g, 0.27 mmol) in EtOH (5 mL). After 30 min, the reaction mixture was diluted with aqueous 10% citric acid (20 mL), extracted with EtOAc (3 × 10 mL), dried, and evaporated. Precipitation from a mixture of MeOH/DCM/hexanes gave **36**/**36a** (89 mg, 77%) as a red solid, mp 110−113 °C. R_f (1:4 MeOH/DCM) 0.25. IR (ATR) ν_{max} cm^{-1}: 3500−2500 (OH), 1639 (C═O). ^1H NMR (600 MHz, DMSO-d_6): δ 8.12 (m [app. d], J = 5.4 Hz, 1H, ArH), 7.94 (m [app. dd], J_1 = 4.2, J_2 = 1.8 Hz, 1H, ArH), 7.81 (d, J = 7.2 Hz, 1H, ArH), 7.77−7.67 (m, 2H, ArH), 7.67−7.55 (m, 2H, ArH), 7.34 (dd [app. t], $J_1 = J_2$ = 7.2 Hz, 2H, PhH), 7.26 (m, 3H, PhH), 5.62 (s, 2H, CH_2). ^{13}C NMR (150 MHz, DMSO-d_6): δ 180.5 (C4), 171.9 (C9), 151.0 (C2), 149.3 (C2′), 137.5, 134.1, 133.6, 133.1, 132.7, 128.7 (PhH), 127.3 (PhH), 126.8 (PhH), 125.6, 124.4, 124.1, 122.3, 101.6 (C3), 46.2 (CH_2). HRMS (ESI^-): calcd for $C_{25}H_{15}N_2O_5^-$ $[M - H]^-$, 423.0989; found, 423.0986.

*6-Benzyl-7-hydroxybenzo[c]pyrrolo[4,3,2-mn]acridin-5(6H)-one (**37**).* Iron powder (0.19 g, 3.4 mmol) was added to a vigorously stirred solution of **36** (0.13 g, 0.31 mmol) in AcOH (7 mL), H_2O (3 mL), and MeOH (2 mL). After 2.5 h, the reaction mixture was diluted with H_2O (20 mL), extracted with EtOAc (3 × 20 mL), dried, and evaporated. Precipitation from a mixture of MeOH/DCM/hexanes followed by recrystalization from EtOH gave **37** (74 mg, 63%) as a purple solid, mp 262−265 °C. R_f (1:19 MeOH/DCM) 0.25. IR (ATR) ν_{max} cm^{-1}: 3200−2800 (OH), 1661 (C═O), 1606 (C═O). ^1H NMR (600 MHz, DMSO-d_6): δ 7.87 (dd, J_1 = 7.2, J_2 = 3.0 Hz, 2H, ArH), 7.75 (d, J = 7.8 Hz, 1H, ArH), 7.64 (dd [app. t], $J_1 = J_2$ = 7.8 Hz, 1H, ArH), 7.58 (dd [app. t], $J_1 = J_2$ = 7.8 Hz, 1H, ArH), 7.33 (m, 3H, ArH), 7.30−7.24 (m, 4H, ArH), 7.21 (dd [app. t], $J_1 = J_2$ = 7.2 Hz, 1H, ArH), 5.52 (s, 2H, CH_2). ^{13}C NMR (150 MHz, DMSO-d_6): δ 181.3 (C7), 159.7 (C5), 139.4 (C11b), 135.0, 133.9, 133.3, 132.6, 131.8, 130.5, 129.0, 128.7 (PhH), 127.8 (PhH), 127.3, 126.9, 126.0, 125.8, 125.3, 124.9, 123.0, 122.9, 101.4 (C4b), 45.2 (CH_2). HRMS (ESI): calcd for $C_{25}H_{17}N_2O_2^+$ $[M + H]^+$, 377.1296; found, 377.1285.

*2,2-Diethoxy-N-methylethanamine (**42**).* Bromoacetaldehyde diethyl acetal (15 mL, 97 mmol) was added to a stirred solution of 40% aqueous $MeNH_2$ (90 mL, 0.11 mol) in MeOH (120 mL). The reaction mixture was heated under gentle reflux for 12 h before being cooled, diluted with brine (150 mL), and extracted with EtOAc (3 × 100 mL). The extracts were washed with brine and evaporated. Distillation of the residue at reduced pressure gave the secondary amine **42** as a clear, colorless oil (13.9 g, 94%), bp 77−79 °C@20 mm Hg. ^1H NMR (400 MHz, $CDCl_3$): δ 4.50 (t, J = 5.6 Hz, 1H, H2) 3.67−3.55 (m, 2H, CH_2O), 3.51−3.40 (m, 2H, CH_2O), 2.60 (d, J = 5.6 Hz, 2H, H1), 2.35 (s, 3H, NMe), 1.12 (t, J = 7.1 Hz, 6H, 2× CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 101.9 (C2), 62.2 (2× CH_2O), 54.1 (C1), 36.3 (NCH_3), 15.2 (2× CH_3). The synthesis of this compound has been described previously, but not by this method, and NMR data have not been reported.[50]

*N-(2,2-Diethoxyethyl)-2,5-dimethoxy-N-methylbenzamide (**43**).* A solution of 2,5-dimethoxybenzoic acid (**41**)[26] (5.71 g, 31.3 mmol) and $SOCl_2$ (10 mL, 0.14 mol) in DCM (25 mL) was heated under reflux for 2 h before the solvent and excess $SOCl_2$ were evaporated. The residue was cooled to 0 °C, and a solution of pyridine (10 mL, 0.12 mol) in DCM (10 mL) was added dropwise, followed by the dropwise addition of a solution of **42** (7.32 g, 49.7 mmol) in DCM (10 mL). The mixture was stirred at room temperature (rt) for 3 h before being diluted with H_2O (50 mL) and extracted with DCM (3 × 20 mL). The extract was washed with sat. aq $NaHCO_3$ (20 mL), dried, and evaporated, and the crude product was subjected to flash chromatography. Elution with 2:3 EtOAc/hexanes gave **43** (9.25 g, 95%) as a clear colorless oil. R_f (3:2 EtOAc/hexanes) 0.35. IR (ATR) ν_{max} cm^{-1}: 1634 (C═O). ^1H NMR (600 MHz $CDCl_3$; a 9:5 mixture of major and minor* rotamers): δ 6.87−6.80 (m, 2H, ArH), 6.78 *(d, J = 3.0 Hz, 1H, ArH), 6.76 (d, J = 3.0 Hz, 1H, ArH), 4.80 (t, J = 5.4 Hz, 1H, H2′), 4.42 *(t, J = 5.4 Hz, 1H, H2′), 3.81−3.77 (m, 2H, OCH_2CH_3), 3.76 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.74 *(s, 3H, OMe), 3.65−3.58 (m, 3H, OCH_2CH_3 & H1′), 3.57−3.50 *(m, 2H, OCH_2CH_3), 3.57−3.50 (m, 1H, H1′), 3.33 *(m, 2H, OCH_2CH_3), 3.29−3.26 *(m, 1H, H1′), 3.22−3.19 *(m, 2H, H1′), 3.15 *(s, 3H, NMe), 2.91 (s, 3H, NMe), 1.23 (t, J = 7.2 Hz, 6H, OCH_2CH_3), 1.12 *(t, J = 7.2 Hz, 3H, OCH_2CH_3). ^{13}C NMR (150 MHz): δ 169.6 *(C═O), 169.4 (C═O), 153.8 (C2 or C5), 149.4 (C2 or C5), 149.1 *(C2 or C5), 127.2 (C1), 127.0 *(C1), 115.5 *(ArH), 115.4 (ArH), 113.6 *(ArH), 113.2 (ArH), 112.5 *(ArH), 112.3 (ArH), 102.1 *(C2′), 101.4 (C2′), 63.8 (OCH_2CH_3), 63.6 (OCH_2CH_3), 63.4 *(OCH_2CH_3), 63.2 *(OCH_2CH_3), 56.2 *(OMe), 56.1 (OMe), 55.9 (OMe), 53.6 *(C1′), 51.0 (C1′), 38.4 (NMe), 34.6 *(NMe), 15.5 (OCH_2CH_3), 15.3 *(OCH_2CH_3). HRMS (APCI): calcd for $C_{16}H_{26}NO_5^+$ $[M + H]^+$, 312.1798; found, 312.1805.

*5,8-Dimethoxy-2-methylisoquinolin-1(2H)-one (**44**).* Concentrated H_2SO_4 (10 mL) was added dropwise to neat **43** with stirring at 0 °C. After the addition was complete, the solution was warmed to 40 °C for 24 h under a $CaCl_2$ guard tube. The solution was cooled, carefully neutralized with ice cold sat. aq $NaHCO_3$ (~50 mL), until effervescing ceased, then extracted with EtOAc (3 × 30 mL). The extract was dried and evaporated. Precipitation from EtOAc/hexanes gave **44** as an off-white solid (5.54 g, 96%), mp 143−148 °C. R_f (EtOAc) 0.15. IR (ATR) ν_{max} cm^{-1}: 1654 (C═O). ^1H NMR (600 MHz, DMSO-d_6): δ 7.38 (d, J = 7.8 Hz, 1H, H3), 7.14 (d, J = 9.0 Hz, 1H, H6 or H7), 6.89 (d, J = 9.0 Hz, 1H, H6 or H7), 6.64 (d, J = 7.8 Hz, 1H, H4), 3.84 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.38 (s, 3H, NMe). ^{13}C NMR (150 MHz, DMSO-d_6): δ 160.0 (C1), 153.8 (C5 or C8), 147.5 (C5 or C8), 134.2 (C3), 130.3 (C4a or C8a), 115.6 (C4a or C8a), 113.1 (C6 or C7), 109.2 (C6 or C7), 98.6 (C4), 56.5 (OMe), 56.3 (OMe), 36.9 (NMe). HRMS (APCI): calcd for $C_{12}H_{14}NO_3^+$ $[M + H]^+$, 220.0959; found, 220.0968.

*8-Hydroxy-5-methoxy-2-methylisoquinolin-1(2H)-one (**45**).* Neat **44** (45 mg, 0.20 mmol) was added to pyridine

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hydrochloride*; the mixture was heated under reflux for 10 min before being diluted with H_2O (20 mL), extracted with EtOAc (3 × 10 mL), dried, and evaporated, and the crude product was subjected to flash chromatography. Elution with 3:2 EtOAc/hexanes gave **45** (24 mg, 57%) as an off-white solid, mp 75−78 °C. R_f (2:3 EtOAc/hexanes) 0.25. IR (ATR) ν_{max} cm^{-1}: 3200−2800 (OH), 1657 (C═O). ^1H NMR (600 MHz, DMSO-d_6): δ 12.4 (s, 1H, OH), 7.45 (d, J = 7.2 Hz, 1H, ArH), 7.19 (d, J = 8.4 Hz, 1H, ArH), 6.78 (d, J = 7.2 Hz, 1H, ArH), 6.76 (d, J = 8.4 Hz, 1H, ArH), 3.83 (s, 3H, OMe), 3.52 (s, 3H, NMe). ^{13}C NMR (150 MHz, DMSO-d_6): δ 164.9 (C1), 153.6 (C5 or C8), 145.7 (C5 or C8), 133.1 (ArH), 127.6 (C4a or C8a), 115.5 (ArH), 111.5 (C4a or C8a), 111.4 (ArH), 101.3 (ArH), 56.2 (OMe), 36.0 (NMe). HRMS (APCI): calcd for $C_{11}H_{12}NO_3^+$ $[M + H]^+$, 206.0833; found, 206.0812.

*Pyridine hydrochloride was prepared from pyridine (2 mL) and concentrated HCl (2.5 mL) as detailed in the preparation of **46** below.

*5,8-Dihydroxy-2-methylisoquinolin-1(2H)-one (**46**).* Method 1: Concentrated HCl (25 mL) was added dropwise to pyridine (20 mL) at 0 °C. After the addition was complete, excess H_2O and pyridine were removed by distillation, leaving pyridine hydrochloride as a white solid. Neat **44** (0.58 g, 2.67 mmol) was added, and the mixture was heated under reflux for 20 min, then cooled, diluted with H_2O (30 mL), and extracted with EtOAc (3 × 20 mL). The extract was dried and evaporated to give **46** (0.49 g, 97%) as an off-white solid, mp 180−185 °C. R_f (3:2 EtOAc/hexanes) 0.3. IR (ATR) ν_{max} cm^{-1}: 3200−3000 (OH), 1652 (C═O). ^1H NMR (600 MHz, DMSO-d_6): δ 12.3 (s, 1H, OH), 9.48 (s, 1H, OH), 7.38 (d, J = 7.8 Hz, 1H, ArH), 7.02 (d, J = 8.4 Hz, 1H, ArH), 6.77 (d, J = 7.8 Hz, 1H, ArH), 6.65 (d, J = 8.4 Hz, 1H, ArH), 3.50 (s, 3H, NMe). ^{13}C NMR (150 MHz, DMSO-d_6): δ 164.9 (C1), 152.5 (C5 or C8), 143.5 (C5 or C8), 132.0 (ArH), 126.1 (C4a or C8a), 118.8 (ArH), 111.7 (ArH), 111.2 (C4a or C8a), 101.8 (ArH), 35.7 (NMe). HRMS (APCI): calcd for $C_{10}H_{10}NO_3^+$ $[M + H]^+$, 192.0641; found, 192.0655.

Method 2: Concentrated H_2SO_4 (2 mL) was added dropwise to **49** (205 mg, 0.558 mmol) with stirring at 0 °C. After the addition was complete, the solution was allowed to warm to rt, then stirring was continued at 50 °C overnight. After 20 h, H_2O (5 mL) was added, and the solution was stirred for 1 h before being diluted with water (∼20 mL) and extracted with EtOAc (3 × 20 mL). The extract was dried and evaporated, and the residue was subjected to flash chromatography. Elution with 2:3 EtOAc/hexanes gave **46** (105 mg, 98%) as an off-white solid, which was identical to the material described above. **Note**: several attempts to repeat this outcome resulted in yields in the range 20−30%.

*2-Methylisoquinoline-1,5,8(2H)-trione (**47**).* Ag_2O (2.59 g, 11.2 mmol) was added to a stirred suspension of **46** (0.57 g, 2.47 mmol) and $MgSO_4$ (1.52 g, 12.6 mmol) in Et_2O (50 mL). After 20 min, the mixture was filtered through a plug of Celite and washed with DCM (3 × 10 mL). The volatiles were then removed to give **47** (0.47 g, quant.) as a bright red solid, mp 184−189 °C. R_f (EtOAc) 0.15. IR (ATR) ν_{max} cm^{-1}: 1661 (C═O). ^1H NMR (600 MHz, DMSO-d_6): δ 8.32 (d, J = 6.6 Hz, 1H, ArH), 6.97 (d, J = 9.6 Hz, 1H, ArH), 6.85 (d, J = 9.6 Hz, 1H, ArH), 6.63 (d, J = 6.6 Hz, 1H, ArH), 3 (s, 3H, NMe). ^{13}C NMR (150 MHz, DMSO-d_6): δ 185.4 (C5 or C8), 182.7 (C5 or C8), 157.4 (C1), 147.6 (ArH), 142.7 (C4a or C8a), 140.3 (ArH), 134.9 (ArH), 116.6 (C4a or C8a), 99.3 (ArH), 38.1 (NMe). HRMS (APCI): calcd for $C_{10}H_8NO_3^+$ $[M + H]^+$, 190.0497; found, 190.0499.

*N-(2,2-Diethoxyethyl)-N-methyl-2,5-diacetoxybenzamide (**49**).* A solution of 2,5-diacetoxybenzoic acid (**48**)[33] (0.31 g, 1.29 mmol) and $SOCl_2$ (0.30 mL, 4.1 mmol) in PhMe (20 mL) was heated under reflux for 2 h before the solvent and excess $SOCl_2$ were removed by distillation. The residue was cooled to 0 °C, and a solution of NEt_3 (0.5 mL, 3.61 mmol) in PhMe (10 mL) was added dropwise, followed by the dropwise addition of a solution of **42** (0.25 g, 1.7 mmol) in PhMe (10 mL). The mixture was stirred at rt for another 3 h before being diluted with H_2O (50 mL) and extracted with EtOAc (3 × 20 mL). The extract was washed with sat. aq $NaHCO_3$ (20 mL), dried, and evaporated, and the residue was subjected to flash chromatography. Elution with 2:3 EtOAc/hexanes gave **49** (0.24 g, 50%) as a pale-yellow oil. R_f (3:2 EtOAc/hexanes) 0.35. IR (ATR) ν_{max} cm^{-1}: 1763 (Ac C═O), 1638 (NC═O). ^1H NMR (600 MHz, DMSO-d_6; a 3:2 mixture of major and minor* rotamers): δ 7.29−7.19 (m, 2H, H3/4 both rotamers), 7.17 *(d, J = 2.4 Hz, 1H, H6), 7.12 (d, J = 2.4 Hz, 1H, H6), 4.67 (t, J = 5.4 Hz, 1H, H2′), 4.51 *(t, J = 5.4 Hz, 1H, H2′), 3.65 *(m, 2H, O**CH$_2$**CH$_3$), 3.51 (m, 3H, O**CH$_2$**CH$_3$ & H1′), 3.14 *(d, J = 5.4 Hz, 1H, H1′), 2.98 *(s, 3H, NMe), 2.82 (s, 3H, NMe), 2.27 (s, 3H, Ac Me), 2.22 (s, 3H, Ac Me), 2.19 *(s, 3H, Ac Me), 1.14 (t, J = 6.6 Hz, 6H, OCH$_2$**CH$_3$**), 1.05 *(t, J = 6.6 Hz, 6H, OCH$_2$**CH$_3$**). ^{13}C NMR (150 MHz, DMSO-d_6; a 3:2 mixture of major and minor* rotamers): δ 169.3 (C═O), 169.2 *(C═O), 168.9 (C═O), 168.8 *(C═O), 166.4 *(C═O), 166.0 (C═O), 147.8 (ArO), 147.6 *(ArO), 143.8 (ArO), 143.7 *(ArO), 130.8 (C1), 130.7 *(C1), 124.4 (ArH), 124.3 *(ArH), 123.5 (ArH), 123.4 *(ArH), 121.7 *(ArH), 120.9 (ArH), 100.5 *(C2′), 100.0 (C2′), 62.7 *(OCH$_2$), 61.5 (OCH$_2$), 52.9 *(C1′), 49.3 (C1′), 37.8 (NMe), 33.7 *(NMe), 20.9 (CO**CH$_3$**), 20.8 *(CO**CH$_3$**), 20.6 (CO**CH$_3$**), 20.5 *(CO**CH$_3$**), 15.3 (CH$_2$**CH$_3$**), 15.2 (CH$_2$**CH$_3$**). HRMS (APCI): calcd for $C_{18}H_{26}NO_7^+$ $[M + H]^+$, 368.1712; found, 368.1704.

*7-Chloro-5,8-dihydroxy-2-methylisoquinolin-1(2H)-one (**52a**).* $SOCl_2$ (0.26 mL, 3.6 mmol) was added to a stirred solution of **47** (93 mg, 0.49 mmol) and pyridine (0.40 mL, 4.9 mmol) in PhMe (20 mL) and dimethoxyethane (DME) (5 mL) at 0 °C. The reaction was then heated to 50 °C for 20 min before being cooled, diluted with H_2O (30 mL), and extracted with EtOAc (3 × 10 mL). The extract was dried and evaporated, and the residue was subjected to chromatography. Elution with 1:4 EtOAc/hexanes gave **52a**, containing ∼6% of the regioisomer 6-chloro-5,8-dihydroxy-2-methylisoquinolin-1(2*H*)-one (**52b**) [NMR data not shown], as a yellow oil (89 mg, 80%). R_f (3:2 EtOAc/hexanes) 0.3. IR (ATR) ν_{max} cm^{-1}: 3100−2300 (OH), 1656 (C═O). ^1H NMR (600 MHz, DMSO-d_6): δ 9.97 (s, 1H, OH), 7.46 (d, J = 7.8 Hz, 1H, H3 or H4), 7.11 (s, 1H, H6), 6.79 (d, J = 7.8 Hz, 1H, H3 or H4), 3.53 (s, 3H, NMe). ^{13}C NMR (150 MHz, DMSO-d_6): δ 164.6 (C1), 148.3 (C5 or C8), 143.9 (C5 or C8), 132.8 (ArCH), 126.0 (C4a or C8a), 118.6 (ArH), 114.2 (C7), 112.1 (C4a or C8a), 101.8 (ArH), 36.2 (NMe). HRMS (APCI): calcd for $C_{10}H_9{}^{35}ClNO_3^+$ $[M + H]^+$, 226.0257; found, 226.0265.

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*7-Chloro-2-methylisoquinoline-1,5,8(2H)-trione (**53a**).* Ag_2O (0.40 g, 1.7 mmol) was added to a stirred suspension of **52a** (69 mg, 0.31 mmol) and $MgSO_4$ (0.25 g, 2.1 mmol) in Et_2O (5 mL) and DME (1 mL). After 20 min, the suspension was filtered through a plug of Celite and washed with DCM (3 × 10 mL). The volatiles were then removed to give **53a**, containing ∼6% of the regioisomer 6-chloro-2-methylisoquinoline-1,5,8(2*H*)-trione (**53b**), as a bright red solid (52 mg, 65%), mp 146−150 °C. R_f (1:19 MeOH/DCM) 0.40; IR (ATR) ν_{max} cm^{-1}: 1672 (C═O). ^1H NMR (600 MHz, DMSO-d_6): δ 8.38 (d, J = 6.6 Hz, 1H, H3 or H4), 7.44 (s, 1H, H6), 6.67 (d, J = 6.6 Hz, 1H, H3 or H4), 3.57 (s, 3H, NMe). ^{13}C NMR (150 MHz, DMSO-d_6): δ 182.8 (C5 or C8), 174.5 (C5 or C8), 157.2 (C1), 148.3 (ArH), 146.6 (C4a or C8a), 143.1 (C7), 132.9 (ArH), 116.3 (C4a or C8a), 99.5 (ArH), 38.2 (NMe). HRMS (APCI): calcd for $C_{10}H_7{}^{35}ClNO_3{}^+$ $[M + H]^+$, 224.0112; found, 224.0109.

*6,7-Dichloro-2-methylisoquinoline-1,5,8(2H)-trione (**38**) and 4,6,7-Trichloro-2-methylisoquinoline-1,5,8(2H)-trione (**54**).* A solution of **47** (0.26 g, 1.40 mmol) in Et_2O (5 mL) was added dropwise to a solution of SO_2Cl_2 (0.45 mL, 5.33 mmol) and NEt_3 (0.20 mL, 1.44 mmol) in Et_2O (15 mL). Once the addition was complete, the reaction was heated under reflux for 20 h before being cooled, diluted with H_2O (30 mL), and extracted with EtOAc (3 × 10 mL). The organic component was dried and evaporated, and the crude solid subjected to flash chromatography. Elution with 3:2 EtOAc/hexanes gave **54** as a red solid (25 mg, 6%), mp 216−220 °C. R_f (EtOAc) 0.25. IR (ATR) ν_{max} cm^{-1}: 1688 (C═O). ^1H NMR (600 MHz): δ 7.99 (s, 1H, H3), 3.72 (s, 3H, NMe). ^{13}C NMR (150 MHz): δ 175.2 (C5 or C8), 172.7 (C5 or C8), 156.4 (C1), 146.2 (ArH), 143.7 (C4a or C8a), 140.3 (C6 or C7), 138.9 (C6 or C7), 118.5 (C4a or C8a), 108.5 (C4), 39.4 (NMe). HRMS (APCI): calcd for $C_{10}H_5{}^{35}Cl_3NO_3{}^+$ $[M + H]^+$, 291.9332; found, 291.9330.

Further elution with EtOAc gave **38** (8 mg, 2%) as a red solid, mp 250−254 °C. R_f (1:99 MeOH/DCM) 0.1. ^1H NMR (600 MHz, DMSO-d_6): δ 8.38 (d, J = 6.6 Hz, 1H, H3 or H4), 6.76 (d, J = 6.6 Hz, 1H, H3 or H4), 3.56 (s, 3H, NMe). ^{13}C NMR (150 MHz, DMSO-d_6): δ 176.0 (C5 or C8), 172.5 (C5 or C8), 156.9 (C1), 148.0 (C3 or C4), 143.1 (C4a or C8a), 142.9 (C6 or C7), 138.7 (C6 or C7), 115.7 (C4a or C8a), 100.1 (C3 or C4), 38.1 (NMe). HRMS (APCI): calcd for $C_{10}H_6{}^{35}Cl_2NO_3{}^+$ $[M + H]^+$, 257.9721; found, 257.9719.

*4-Iodo-2,5-dimethoxytoluene (**57**).* I_2 (2.5 g, 10 mmol) was added to a stirred suspension of 2,5-dimethoxytoluene (**55**) (1.25 g, 8.21 mmol) and Ag_2SO_4 (5.4 g, 17 mmol) in EtOH (20 mL). After 24 h, the reaction mixture was filtered, diluted with H_2O (30 mL), and extracted with EtOAc (3 × 20 mL). The extract was dried and evaporated, and the crude product was subjected to flash chromatography. Elution with 1:9 EtOAc/hexanes gave iodide **57** as a white solid (1.76 g, 77%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.17 (s, 1H, H3 or H6), 6.67 (s, 1H, H3 or H6), 3.82 (s, 3H, OMe), 3.77 (s, 3H, OMe), 2.19 (Me). The ^1H NMR data are identical to those reported.[51]

*4-Bromo-2,5-dimethoxybenzoic Acid (**58**).*[38] $KMnO_4$ (2.75 g, 17.4 mmol) was added to a stirred mixture of 1-bromo-2,5-dimethoxy-4-methylbenzene (**56**)[37] (0.73 g, 3.16 mmol) in pyridine (10 mL) and H_2O (10 mL). After 24 h, the reaction mixture was diluted with 1 M HCl (30 mL), extracted with EtOAc (3 × 20 mL), dried, and evaporated to give benzoic acid **58** as a white solid (0.58 g, 70%), which was used without further purification. ^1H NMR (500 MHz, DMSO-d_6): δ 12.81 (br s, CO_2H), 7.37 (s, 1H, H3 or H6), 7.32 (s, 1H, H3 or H6), 3.81 (s, 3H, OMe), 3.78 (s, 3H, OMe). The ^1H NMR spectrum matched the reported data.[52]

*4-Iodo-2,5-dimethoxybenzoic Acid (**59**).* $KMnO_4$ (6.05 g, 38.3 mmol) was added to a stirred mixture of **57** (1.76 g, 6.31 mmol) in pyridine (20 mL) and H_2O (20 mL). After 24 h, the reaction mixture was diluted with 1 M HCl (50 mL) and extracted with EtOAc (3 × 20 mL). The extract was dried and evaporated. Precipitation from EtOAc/hexanes gave benzoic acid **59** as a yellow/white solid (0.69 g, 36%), mp 172−175 °C [lit.[53] 175−177 °C], which was used without further purification in the next step.

*4-Bromo-N-(2,2-diethoxyethyl)-2,5-dimethoxy-N-methylbenzamide (**60**).* A solution of **58** (3.04 g, 11.7 mmol) and $SOCl_2$ (1.5 mL, 21 mmol) in PhMe (40 mL) was heated under reflux for 2 h before the solvent and excess $SOCl_2$ were removed by distillation. The residue was cooled to 0 °C, and a solution of pyridine (1.5 mL, 18 mmol) in PhMe (10 mL) was added dropwise, followed by the dropwise addition of a solution of **42** (2.34 g, 15.9 mmol) in PhMe (10 mL). The mixture was stirred at rt for another 2 h before being diluted with H_2O (50 mL) and extracted with EtOAc (3 × 20 mL). The extract was washed with sat. aq $NaHCO_3$ (20 mL), dried, and evaporated, and the residue was subjected to flash chromatography. Elution with 2:3 EtOAc/hexanes gave tertiary amide **60** (3.1 g, 68%) as a pale-yellow oil. R_f (2:3 EtOAc/hexanes) 0.15. IR (ATR) ν_{max} cm^{-1}: 1635 (C═O). ^1H NMR (600 MHz, DMSO-d_6; a 10:7 mixture of major and minor* rotamers): δ 7.33 (s, 1H, H3 or H6), 7.31 *(s, 1H, H3 or H6), 6.95 *(s, 1H, H3 or H6), 6.89 *(s, 1H, H3 or H6), 4.68 (t, J = 5.4 Hz, 1H, H2′), 4.48 *(t, J = 5.4 Hz, 1H, H2′), 3.78 (s, 3H, OMe), 3.78 *(s, 3H, OMe), 3.75 (s, 3H, OMe), 3.74 *(s, 3H, OMe), 3.71−3.45 (m, 6H, OCH_2CH_3 & H1′), 3.12 *(pseudo dd, J_1 = 6.0 Hz, J_2 = 4.2 Hz, 2H, H1′), 2.99 *(s, 3H, NMe), 2.80 (s, 3H, NMe), 1.15 (pseudo t [app. s], 6H, OCH_2CH_3), 1.04 *(t, J = 6.6 Hz, 6H, OCH_2CH_3). ^{13}C NMR (150 MHz, DMSO-d_6): δ 167.3 *(C═O), 167.2 (C═O), 149.6 (C2 or C5), 149.4 *(C2 or C5), 148.8 (C2 or C5), 148.7 *(C2 or C5), 126.1 (C1), 125.9 *(C1), 116.6 (C3 or C6), 116.4 *(C3 or C6), 112.2 (C4a or C8a), 111.3 (C3 or C6), 111.2 *(C3 or C6), 111.1 (C4a or C8a), 100.8 (C4), 100.7 *(C2′), 100.2 (C2′), 62.6 (OCH_2CH_3), 62.1 *(OCH_2CH_3), 61.8 (OCH_2CH_3), 60.9 *(OCH_2CH_3), 56.6 *(OMe), 56.5 (OMe), 56.3 (OMe), 56.2 *(OMe), 52.6 *(C1′), 49.6 (C1′), 37.3 (NMe), 33.5 *(NMe), 15.2 (OCH_2CH_3), 15.1 *(OCH_2CH_3). HRMS (ESI): calcd for $C_{18}H_{27}{}^{79}BrN_2NaO_5{}^+$ $[M + Na + MeCN]^+$, 453.0986; found, 453.0996.

*N-(2,2-Diethoxyethyl)-4-iodo-2,5-dimethoxy-N-methylbenzamide (**61**).* A solution of **59** (0.69 g, 2.24 mmol) and $SOCl_2$ (5.0 mL, 69 mmol) in PhMe (20 mL) was heated under reflux for 2 h before the solvent and excess $SOCl_2$ were removed by distillation. The residue was cooled to 0 °C, and a solution of NEt_3 (8.0 mL, 58 mmol) in PhMe (10 mL) was added dropwise, followed by the dropwise addition of a solution of **42** (0.62 g, 4.21 mmol) in PhMe (5 mL). The mixture was stirred at rt for another 24 h before being diluted with H_2O (50 mL) and extracted with EtOAc (3 × 20 mL). The extract was washed with sat. aq $NaHCO_3$ (20 mL), dried, and evaporated, and the residue was subjected to

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flash chromatography. Elution with 1:4 EtOAc/hexanes gave tertiary amide **61** (0.81 g, 82%) as a pale-yellow oil. R_f (2:3 EtOAc/hexanes) 0.15. IR (ATR) ν_{max} cm^{-1}: 1630 (C═O). ^1H NMR (600 MHz—isolated as a mixture of rotamers, with signals due to the minor rotamer denoted by asterisks): δ 7.32 (s, 1H, H3 or H6), 7.31 *(s, 1H, H3 or H6), 6.75 *(s, 1H, H3 or H6), 6.72 (s, 1H, H3 or H6), 4.80 (t, J = 5.4 Hz, 1H, H2′), 4.46 *(t, J = 5.4 Hz, 1H, H2′), 3.83 (s, 3H, OMe), 3.82 *(s, 3H, OMe), 3.78 (s, 3H, OMe), 3.77 *(s, 3H, OMe), 3.72−3.42 (m, 6H, O**CH$_2$**CH$_3$ & H1′), 3.38 *(m, 2H, O**CH$_2$**CH$_3$), 3.34−3.27 *(m, 1H, H1′), 3.24−3.17 *(m, 1H, H1′), 3.15 *(s, 3H, NMe), 2.92 (s, 3H, NMe), 1.24 (t, J = 7.2 Hz, 6H, OCH$_2$**CH$_3$**), 1.15 *(t, J = 7.2 Hz, 6H, OCH$_2$**CH$_3$**). ^{13}C NMR (150 MHz): δ 168.9 *(C═O), 168.7 (C═O), 152.9 (C2 or C5), 152.8 *(C2 or C5), 149.7 (C2 or C5), 149.5 *(C2 or C5), 127.2 (C1), 127.0 *(C1), 122.8 *(C3 or C6), 122.7 (C3 or C6), 110.8 *(C3 or C6), 110.3 (C3 or C6), 101.6 *(C2′), 101.2 (C2′), 86.7 (C4), 86.6 *(C4), 63.4 (O**CH$_2$**CH$_3$), 63.0 (O**CH$_2$**CH$_3$), 61.8 *(O**CH$_2$**CH$_3$), 60.5 *(O**CH$_2$**CH$_3$), 57.1 (OMe), 57.0 *(OMe), 56.5 *(OMe), 56.4 (OMe), 53.5 *(C1′), 50.9 (C1′), 38.3 (NMe), 34.3 *(NMe), 15.5 (OCH$_2$**CH$_3$**), 15.3 *(OCH$_2$**CH$_3$**). HRMS (APCI): calcd for $C_{16}H_{25}INO_5^+$ $[M + H]^+$, 438.0790; found, 438.0772.

*6-Bromo-5,8-dimethoxy-2-methylisoquinolin-1(2H)-one (**62**) and 6-Bromo-5-hydroxy-8-methoxy-2-methylisoquinolin-1(2H)-one (**64**).* Concentrated H_2SO_4 (10 mL) was added dropwise to **60** (3.05 g, 7.82 mmol) with stirring at 0 °C under $CaCl_2$ guard. After the addition was complete, the solution was allowed to warm to rt, then stirred at 50 °C for 24 h, before being diluted with H_2O (30 mL), carefully neutralized with ice-cold sat. aq $NaHCO_3$ (∼50 mL), then extracted with EtOAc (3 × 20 mL). The extract was dried and evaporated. Precipitation from EtOAc followed by recrystallization from MeOH gave **64** as white plates (0.24 g, 11%), mp 194−197 °C. R_f (1:19 MeOH/DCM) 0.15. IR (ATR) ν_{max} cm^{-1}: 3300−2700 (OH), 1643 (C═O). ^1H NMR (600 MHz, DMSO-d_6): δ 9.28 (s, 1H, OH), 7.46 (d, J = 7.8 Hz, 1H, H3), 7.05 (s, 1H, H7), 6.67 (d, J = 7.8 Hz, 1H, H4), 3.77 (s, 3H, OMe), 3.38 (s, 3H, NMe). ^{13}C NMR (150 MHz, DMSO-d_6): δ 158.9 (C1), 153.5 (C2 or C5), 141.6 (C2 or C5), 134.4 (C3), 131.2 (C4a or C8a), 114.6 (C4a or C8a), 113.9 (C6), 112.2 (C7), 98.4 (C4), 56.3 (OMe), 36.3 (NMe). HRMS (ESI): calcd for $C_{13}H_{13}{}^{79}BrN_2NaO_3^+$ $[M + Na + MeCN]^+$, 347.0005; found, 347.0002.

The filtrate was evaporated to give isoquinolone **62** as a pale-yellow solid (1.67 g, 72%), mp 118−120 °C. R_f (1:19 MeOH/DCM) 0.35. IR (ATR) ν_{max} cm^{-1}: 1656 (C═O). ^1H NMR (600 MHz, DMSO-d_6): δ 7.54 (d, J = 7.8 Hz, 1H, H3), 7.11 (s, 1H, H7), 6.52 (d, J = 7.8 Hz, 1H, H4), 3.83 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.40 (s, 3H, NMe). ^{13}C NMR (150 MHz): δ 158.9 (C1), 156.7 (C2 or C5), 144.4 (C2 or C5), 135.9 (C3), 134.4 (C4a or C8a), 119.8 (C4a or C8a), 114.8 (C6), 111.8 (C7), 97.6 (C4), 61.0 (OMe), 56.3 (OMe), 36.5 (NMe). HRMS (ESI): calcd for $C_{12}H_{13}{}^{79}BrNO_3^+$ $[M + H]^+$, 298.0095; found, 298.0073.

*6-Iodo-5,8-dimethoxy-2-methylisoquinolin-1(2H)-one (**63**) and 5-Hydroxy-6-iodo-8-methoxy-2-methylisoquinolin-1(2H)-one (**65**).* Concentrated H_2SO_4 (10 mL) was added dropwise to **61** (0.81 g, 1.85 mmol) with stirring at 0 °C under $CaCl_2$ guard. After the addition was complete, the solution was allowed to warm to rt, and stirring was continued at 60 °C for 24 h, before the reaction mixture was diluted with H_2O (30 mL), carefully neutralized with ice cold sat. aq $NaHCO_3$ (∼50 mL), then extracted with EtOAc (3 × 20 mL). The extract was dried and evaporated, and the residue was subjected to flash chromatography. Elution with EtOAc gave isoquinolone **63** as a pale-yellow solid (0.18 g, 28%), mp 50−52 °C. R_f (1:19 MeOH/DCM) 0.3. IR (ATR) ν_{max} cm^{-1}: 1647 (C═O). ^1H NMR (500 MHz, DMSO-d_6): δ 7.50 (d, J = 9.0 Hz, 1H, H3), 7.23 (s, 1H, H7), 6.47 (d, J = 9.0 Hz, 1H, H4), 3.80 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3.38 (s, 3H, NMe). ^{13}C NMR (125 MHz, DMSO-d_6): δ 159.1 (C1), 156.6 (C2 or C5), 147.8 (C2 or C5), 135.8 (C3), 133.1 (C4a or C8a), 117.3 (C7), 115.4 (C4a or C8a), 98.0 (C4), 96.6 (C6), 61.0 (OMe), 56.3 (OMe), 36.6 (NMe). HRMS (APCI): calcd for $C_{12}H_{13}INO_3^+$ $[M + H]^+$, 345.9938; found, 345.9935.

Further elution gave **65** (0.26 g, 42%) as a yellow/orange solid, mp 163−166 °C. R_f (1:19 MeOH/DCM) 0.2. IR (ATR) ν_{max} cm^{-1}: 3700−2700 (OH), 1646 (C═O). ^1H NMR (500 MHz, DMSO-d_6): δ 9.25 (s, 1H, OH), 7.45 (d, J = 9.0 Hz, 1H, H3), 7.21 (s, 1H, H7), 6.65 (d, J = 9.0 Hz, 1H, H4), 3.76 (s, 3H, OMe), 3.38 (s, 3H, NMe). ^{13}C NMR (125 MHz, DMSO-d_6): δ 159.2 (C1), 153.8 (C2 or C5), 144.8 (C2 or C5), 134.4 (C3), 129.9 (C4a or C8a), 118.0 (C7), 115.3 (C4a or C8a), 98.7 (C4), 91.9 (C6), 56.4 (OMe), 36.5 (NMe). HRMS (APCI): calcd for $C_{11}H_{11}INO_3^+$ $[M + H]^+$, 331.9796; found, 331.9778.

*6-Bromo-2-methylisoquinoline-1,5,8(2H)-trione (**67**).* A solution of CAN (0.29 g, 0.53 mmol) in H_2O (1 mL) was added to a stirred solution of **64** (28 mg, 99 μmol) in MeCN (8 mL) at −30 °C. The reaction was allowed to warm to −20 °C over 30 min before being diluted with H_2O (20 mL) and extracted with EtOAc (3 × 10 mL). The extract was dried and evaporated to give quinone **67** as a red solid (20 mg, 76%), mp 167−171 °C. R_f (1:19 MeOH/DCM) 0.15. IR (ATR) ν_{max} cm^{-1}: 1678 (C═O). ^1H NMR (600 MHz, DMSO-d_6): δ 8.31 (d, J = 7.2 Hz, 1H, H3), 7.45 (s, 1H, H7), 6.71 (d, J = 7.2 Hz, 1H, H4), 3.52 (s, 3H, NMe). ^{13}C NMR (150 MHz): δ 180.2 (C5 or C8), 178.4 (C5 or C8), 157.3 (C1), 147.4 (C3), 142.6 (C4a or C8a), 141.2 (C7), 134.0 (C4a or C8a), 116.2 (C6), 100.4 (C4), 38.1 (NMe).

*6-Iodo-2-methylisoquinoline-1,5,8(2H)-trione (**68**).* A solution of CAN (1.65 g, 3.01 mmol) in H_2O (2 mL) was added to a stirred solution of **65** (0.18 g, 0.54 mmol) in MeCN (12 mL) at −30 °C. The reaction was allowed to warm to −20 °C over 20 min before being diluted with H_2O (20 mL) and extracted with EtOAc (3 × 10 mL). The extract was dried and evaporated to give quinone **68** as a red solid (0.10 g, 59%), mp 218−220 °C. R_f (EtOAc) 0.1. IR (ATR) ν_{max} cm^{-1}: 1683 (C═O). ^1H NMR (600 MHz, DMSO-d_6): δ 8.27 (d, J = 6.6 Hz, 1H, H3), 7.69 (s, 1H, H7), 6.69 (d, J = 6.6 Hz, 1H, H4), 3.51 (s, 3H, NMe). ^{13}C NMR (150 MHz, DMSO-d_6): δ 180.1 (C5 or C8), 179.9 (C5 or C8), 157.4 (C1), 148.9 (C3), 147.3 (C7), 141.3 (C4a or C8a), 116.5 (C4a or C8a), 116.3 (C6), 100.8 (C4), 38.1 (NMe). HRMS (APCI): calcd for $C_{10}H_7INO_3^+$ $[M + H]^+$, 315.9476; found, 315.9465.

*Ethyl 2-(5,8-Dihydroxy-2-methyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-2-(2-nitrophenyl)acetate (**70**).* K_2CO_3 (0.21 g, 1.54 mmol) was added to a stirred solution of **67** (92 mg, 0.34 mmol) and **15** (0.18 g, 0.87 mmol) in DMF (5 mL). The reaction was heated to 45 °C and maintained for 2 h before being cooled, diluted with 1 M HCl (20 mL), and

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extracted with EtOAc (3 × 10 mL). The extract was dried and evaporated, and the residue was subjected to flash chromatography. Elution with 3:2 EtOAc/hexanes gave **70** as a yellow-orange solid (39 mg, 29%). ^{1}H NMR (600 MHz): δ 13.10 (s, 1H, OH), 8.07 (d, J = 7.2 Hz, 1H, H3″), 7.44 (dd, J_1 = J_2 = 7.2 Hz, 1H, H4″ or H5″), 7.42 (dd, J_1 = J_2 = 7.2 Hz, 1H, H4″ or H5″), 7.22 (d, J = 7.2 Hz, 1H, H6″), 7.09 (d, J = 7.2 Hz, 1H, H3′), 6.91 (d, J = 7.2 Hz, 1H, H4′), 6.34 (s, 1H, H2 or H7′), 5.52 (s, 1H, H2 or H7′), 4.22 (q, J = 6.6 Hz, 2H, OCH_2CH_3), 3.61 (s, 3H, NMe), 1.20 (t, J = 6.6 Hz, 3H, OCH_2CH_3). ^{13}C NMR (150 MHz): δ 170.4 (C1), 165.3 (C1′), 153.3 (C5′ or C8′), 149.8 (C5′ or C8′), 138.7 (C2″), 133.3 (ArH), 133.2, 132.5, 130.7 (ArH), 128.3 (ArH), 126.4, 125.1, 125.0 (ArH), 119.2, 110.9, 102.5 (ArH), 61.9 (OCH_2CH_3), 47.1 (C2), 36.7 (NMe), 14.0 (OCH_2CH_3).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c02116.

CIF file for the crystal structure of **35**/**35a** (CIF)
CIF file for the crystal structure of **53a**/**53b** (CIF)
CIF file for the crystal structure of **64** (CIF)
CIF file for the crystal structure of **68** (CIF)
^{1}H and ^{13}C spectra annotated with skeleton-numbered structures and general crystallographic methods, tabulated data, and CCDC deposit numbers for compounds **35**/**35a**, **53a**/**53b**, **64**, and **68** (PDF)

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Notes

The authors declare no competing financial interest.

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